Reply to Letter: "Accelerated Liver Hypertrophy: ALPPS and More!"

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DOI: https://doi.org/10.1097/SLA.0000000000000609

RALPP could significantly increase the FLR by a median of 62.3% (range, 53.1%–95.4%) in a much shorter length of time (mean = 21.8 ± 9.4 days) than by PVE, which increased the FLR by a median of 24.6% (range, 8.4%–35.4%) after 55.4 ± 15.6 days, reflecting a significant gain of FLR by 38.0% ($P = 0.0079$) with a significant reduction of 34 days to achieve this ($P = 0.003$) (Figs. 1, 2). There was no difference in liver function between the 2 groups on days 1 to 5 posthepatectomy.

ALPPS is superior to PVE in terms of FLR but is associated with a greater morbidity and mortality, particularly from bile leaks and hemorrhage after the initial procedure.[4–8] In the current RALPP study, a high hypertrophy rate of 62.3%, similar to ALPPS,[4,5] was achieved with no mortality and a morbidity rate of 20.0%. No bile leaks were seen in patients on liver resection after RALPP. The hypertrophy rate is far greater than that reported in PVE studies and, indeed, in this case-controlled study, where the FLR was analyzed with the same method of volume calculation. The physiological mechanism for this greater increase in FLR is not known but may be in response to surgical trauma and a complete transection of the parenchyma, thereby stopping any cross-portal circulation. Both these mechanisms may create a regeneration stimulus. The rapid regeneration response of a mean of 21.8 days in our study and 9 days in the original ALPPS article has certain benefits.[5] Importantly, there is less time for additional micro- and macro-metastatic diseases to develop. Indeed, in 12.0% of patients, hepatic resection after PVE is not possible due to tumor progression,[3] thought to be due to a more rapid growth of tumor than liver parenchyma after PVE.[11] Whether this is significantly improved with ALPPS must be determined in an awaited clinical trial. The major drawback to ALPPS is the high morbidity rate, in particular from bile leaks, and an increased mortality rate. We believe that RALPP is a better alternative than ALPPS because it limits the invasiveness of the first stage of the procedure while capitalizing on the liver hypertrophy without high morbidity and mortality rates associated with ALPPS. It can easily be performed laparoscopically and can be performed at the same time as a stage 1 liver resection for patients with bilobar disease.

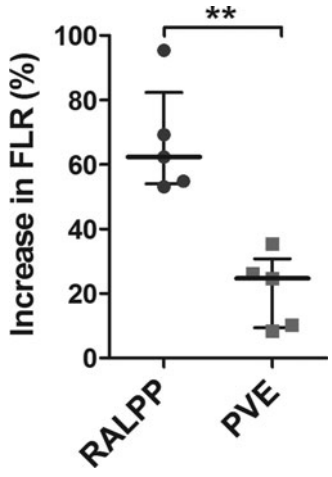

FIGURE 1. The percentage increase in the size of the FLR after both RALPP and PVE (median, error bars depict the range). $^{**}P = 0.0079$, calculated using the Mann-Whitney *U* test.

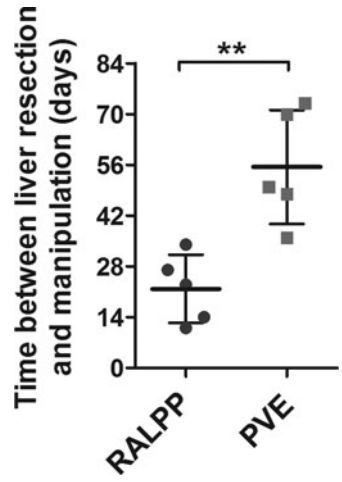

FIGURE 2. The number of days between either RALPP or PVE and completion hepatectomy (median, error bars depict the standard deviation. $^{**}P = 0.003$, calculated using the Student *t* test (2-tailed).

Although only 5 patients were reported here who had undergone RALPP, it has been demonstrated that it is a feasible and safe alternative to ALPPS to achieve a rapid liver regeneration in the contralateral lobe of the liver without the increased morbidity and mortality associated with ALPPS. We are setting up a randomized controlled trial to further evaluate the technique compared with PVE and ALPPS.

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Reply:

We present 3 letters to the editor in response to an original contribution by Schnitzbauer et al.[1] This inaugural article introduced a novel method to induce liver

Disclosure: The authors declare no conflicts of interest.
DOI: 10.1097/SLA.0000000000000609

hypertrophy of the liver remnant for patients with extensive tumor load by performing surgery in 2 stages with ligation of the right portal vein and parenchymal transection, together with cleaning of tumors from the left side of the liver in a first stage, followed in a second stage by the completion hepatectomy of the right side. The operation has become known as "ALPPS" (*A*ssociating *L*iver *P*artition with *P*ortal vein ligation for *S*taged hepatectomy).[2] ALPPS has attracted intense interest, as reflected by a series of letters published in the journal[3–6] and other case reports published elsewhere.[7–12] The discussion has focused on the safety of the procedure because of reported higher mortality and morbidity rates than those reported by conventional approaches.[13,14] Three letters proposing modifications to the initial ALPPS procedure with the goal to increase safety and avoid postoperative liver failure are presented.

The letter by Lau et al is based on the hypothesis that the rapid volume increase in ALLPS does not represent function and that a functional assessment of the liver remnant as a "safety check" could prevent postoperative liver dysfunction and mortality. They intraoperatively assessed function of the isolated liver remnant using indocyanine green clearance (ICG) of the liver remnant during stages 1 and 2 by clamping the right hepatic artery and the right portal vein. They observed that 2 weeks after stage 1, ICG clearance of the liver remnant improves from values considered to be unsafe for liver resection to acceptable values. The authors do not explain, however, how they select their intraoperative threshold of ICG retention of 4.8% at 15 minutes to safely proceed with resection. We know from existing literature that, in cirrhotic livers, a rate of retention of ICG of less than 14% at 15 minutes is acceptable to proceed with removal of more than 50% liver tissue.[15] Which cutoff offers the potential to abort the completion hepatectomy at stage 2 resection, and thereby prevent liver failure, remains unclear in this report of 1 case. Although the method holds promise, there remains some doubt about standardization because ICG clearance depends on portal flow, which may vary considerably intraoperatively and, moreover, has not been validated in the setting of ALPPS.

Two other letters recommend technical modifications to ALPPS to improve safety of the procedure. Gall et al propose to replace parenchymal transection during stage 1 with the use of lined up laparoscopic radio-frequency probes to produce a necrosis zone of 1 cm width. This approach used in 5 patients induced rapid hypertrophy in the range of those observed in the standard ALPPS approach. They label this modification "RALPP" (*R*adio-frequency–*A*ssisted *L*iver *P*artition with *P*ortal vein ligation). They were able to complete both stages laparoscopically with no mortality. On the same line, Gringeri et al report the use of microwave ablation for stage 1, also performed laparoscopically, to create a "necrotic groove" between the right and left sides of the liver by repeated and stepwise application in 1 patient. They observed a doubling of the liver remnant in 10 days and performed stage 2 with only minor complications. They nicknamed their procedure "LAPS" (associating *L*aparoscopic microwave *A*blation with *P*ortal vein ablation for *S*taged hepatectomy). The authors of both letters mention that they will proceed with a prospective evaluation of their modifications.

Although these concepts appropriately look for improved safety in the procedure, including the element of laparoscopy, we would like to highlight a few points. First, the promises of safety in case reports or small series could easily be disappointed in larger prospective studies. Second, authors are tempted to draw early mechanistic conclusions about rapid growth simply because vascular flow between the 2 liver sides is abrogated in ALPPS, and also in RALPP and LAPS, although this might not be the full story. Other mechanisms boosting regeneration, under investigation in a few laboratories, may be involved. While we enthusiastically welcome the new members into the ALPPS family, we should focus now on investigating the underlying mechanisms behind this rapid hypertrophy and from such knowledge develop new and safer strategies.

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